Anatomic pathology selected abstracts

Editors: Rouzan Karabakhtsian, MD, PhD, professor of pathology and director of the Women's Health Pathology Fellowship, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY; Shaomin Hu, MD, PhD, staff pathologist, Cleveland Clinic; S. Emily Bachert, MD, breast pathology fellow, Brigham and Women's Hospital, Boston; and Amarpreet Bhalla, MD, assistant professor of pathology, Albert Einstein College of Medicine, Montefiore Medical Center.

Histological regression in melanoma: impact on SLN status and survival

April 2022—Regression in melanoma is an immunological phenomenon that results in vascular fibrous tissue partially or completely replacing the tumor and is often accompanied by pigment-laden macrophages and chronic inflammation. In many cases, tumor-infiltrating lymphocytes (TILs), which permeate the tumor and disrupt nests or directly appose tumor cells, represent the earliest phase of this process. The prognostic significance of regression has long been debated, with inconsistent findings reported in the literature. The authors conducted a study to determine whether regression in primary cutaneous melanomas predicted sentinel lymph node status and survival outcomes in a large cohort of patients managed at a single medical center in Australia. Clinical and pathological parameters for 8,693 consecutive cases were retrieved for the study. Associations between regression and sentinel lymph node status, overall survival, melanoma-specific survival, and recurrence-free survival were investigated using logistic and Cox regression. Histological evidence of regression was present in 1,958 (22.5 percent) cases. Regression was significantly associated with lower Breslow thickness, lower mitotic rate, and absence of ulceration ($p<0.0001$). Multivariable analysis showed that regression in combination with TILs independently predicted a negative sentinel lymph node biopsy (odds ratio, 0.33; 95 percent confidence interval [CI], 0.20–0.52; $p<0.0001$). Patients whose tumors showed regression and TILs had the highest 10-year overall survival (65 percent), melanoma-specific survival (85 percent), and recurrence-free survival (60 percent). On multivariable analysis, the concurrent presence of regression and TILs independently predicted the lowest risk of death from melanoma (hazard ratio, 0.69; 95 percent CI, 0.51–0.94; $p=0.0003$) and the lowest rate of disease recurrence (hazard ratio, 0.71; 95 percent CI, 0.58–0.85; $p<0.0001$). However, in the subgroup analysis of stage III patients, regression predicted the lowest overall and recurrence-free survival, with melanoma-specific survival showing a similar trend. The findings indicate that regression plays a prognostically favorable role in primary cutaneous melanoma. However, in stage III melanoma patients, regression may be a marker of more aggressive disease.

Aivazian K, Ahmed T, El Sharouni MA, et al. Histological regression in melanoma: impact on sentinel lymph node status and survival. *Mod Pathol*. 2021;34(11):1999–2008.

Correspondence: Dr. Richard Scolyer at richard.scolyer@health.nsw.gov.au

CERTAIN study results: use of adjunctive p16 IHC in cervical biopsies

The Lower Anogenital Squamous Terminology (LAST) Project recommends using p16 IHC as an adjunct to morphologic assessment of cervical biopsies according to a specific set of criteria. The authors analyzed the effect of adjunctive p16 according to LAST criteria in a U.S.-based diagnostic utility study involving 70 surgical pathologists who provided a cumulative total of 38,500 reads on cervical biopsies. Compared with the results obtained using only H&E-stained slides, adding p16-stained slides per LAST criteria increased the sensitivity and specificity for diagnosing histologic high-grade squamous intraepithelial lesions across all cases by 8.1 percent (95 percent confidence interval [CI], 6.5–9.7; $P<0.0001$) and 3.5 percent (95 percent CI, 2.8–4.2; $P<0.0001$), respectively, using expert consensus diagnoses on H&E plus p16 as a reference. Within the subset of cases classified by the pathologists as fulfilling the LAST criteria, adding p16 increased sensitivity by 11.8 percent (95 percent CI, 9.5–14.0; $P<0.0001$) and specificity by 9.7 percent (95 percent CI, 7.8–11.5; $P<0.0001$). However, a comparable improvement in sensitivity (11.0 percent; 95 percent CI, 7.8–14.1; $P<0.0001$) was found when p16 was used in cases in which p16 staining was not ordered by the pathologists per LAST, whereas specificity decreased by 0.8 percent (95 percent CI, -1.1 to -0.5; $P<0.0001$) in these cases. The study demonstrated a clinically and

statistically significant increase in sensitivity and specificity for high-grade squamous intraepithelial lesion when p16 was used according to LAST criteria. Extending the use of p16 to non-LAST cases led to a comparable improvement in sensitivity within this subgroup of biopsies at the cost of a minimal but statistically significant difference in specificity.

Wright Jr TC, Stoler MH, Ferenczy A, et al. The CERTAIN study results: adjunctive p16 immunohistochemistry use in cervical biopsies according to LAST criteria. *Am J Surg Pathol*. 2021;45:1348–1356.

Correspondence: Dr. Thomas C. Wright Jr. at tcw1@columbia.edu

Measurement of depth of invasion vs. tumor thickness in early oral tongue squamous cell carcinoma

The eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual introduced depth of invasion into the pT category of oral cavity squamous cell carcinoma. However, the authors of this study noted multiple practical obstacles that hindered accurate measurement of depth of invasion in their daily practice. To compare the prognostic effects of depth of invasion and tumor thickness, the authors conducted a pathology review of a retrospective cohort of 293 patients with pT1/T2 oral tongue squamous cell carcinoma, as defined by the AJCC cancer staging manual seventh edition. Overall survival and nodal metastasis rate at initial resection were the primary and secondary outcomes, respectively. The authors found that tumor thickness and depth of invasion were highly correlated (correlation coefficient, 0.984). They also found that the upstage rate was only six percent (18 of 293 patients) when using tumor thickness in lieu of depth of invasion in the pT stage. More importantly, depth of invasion and tumor thickness, as well as pT stage using depth of invasion and tumor thickness, performed identically in predicting risk of nodal metastasis and overall survival. Therefore, the authors propose replacing depth of invasion, a complicated measurement with many challenges, with tumor thickness in the pT staging system.

Salama AM, Valero C, Katabi N, et al. Depth of invasion versus tumour thickness in early oral tongue squamous cell carcinoma: which measurement is the most practical and predictive of outcome? *Histopathology*. 2021;79(3):325–337.

Correspondence: Dr. Bin Xu at xub@mskcc.org

Loss of expression of YAP1 C-terminus as an ancillary marker for EHE variant with *YAP1-TFE3* fusion

Epithelioid hemangioendothelioma (EHE) with *YAP1-TFE3* fusion is a recently characterized distinctive variant of EHE that accounts for less than five percent of cases. It is composed of nests of epithelioid cells with voluminous pale cytoplasm and often shows focally vasoformative architecture. While TFE3 IHC can be used to support the diagnosis, studies have questioned its specificity. Yes-associated protein 1 (YAP1), part of the Hippo signaling pathway, is expressed in normal endothelial cells but becomes disrupted in the EHE variant with *YAP1-TFE3*, such that only a small N-terminal region of YAP1 is expressed in the fusion protein. A recent study reported *YAP1* rearrangements in a subset of retiform and composite hemangioendotheliomas (RHE and CHE, respectively). The authors conducted a study in which they evaluated the diagnostic utility of an antibody directed against the C-terminus of YAP1 (YAP1-CT) for EHE with *YAP1-TFE3*, RHE, and CHE. The study included 78 tumors: EHE variant with *YAP1-TFE3* (n=13), conventional (CAMTA1-positive) EHE (n=20), pseudomyogenic hemangioendothelioma (n=10), epithelioid hemangioma (n=19), epithelioid angiosarcoma (n=10), RHE (n=4), and CHE (n=2). IHC was performed using a rabbit monoclonal anti-YAP1 C-terminus antibody. EHE variant showed complete loss of YAP1-CT expression in 10 of 13 (77 percent) cases. All cases of RHE and CHE with previously confirmed *YAP1* rearrangements also showed loss of YAP1-CT expression. Loss of YAP1-CT was seen in one conventional EHE (one of 20; five percent). All other epithelioid vascular tumors retained YAP1-CT expression. Loss of YAP1-CT expression appears to be associated with good sensitivity and specificity for the EHE variant with *YAP1-TFE3* fusion and, along with TFE3 and CAMTA1 IHC, may provide additional support in challenging cases. This marker also may be useful in

the diagnosis of RHE and CHE.

Anderson WJ, Fletcher CDM, Hornick JL. Loss of expression of YAP1 C-terminus as an ancillary marker for epithelioid hemangioendothelioma variant with *YAP1-TFE3* fusion and other YAP1-related vascular neoplasms. *Mod Pathol*. 2021;
34(11):2036–2042.

Correspondence: Dr. J. L. Hornick at jhornick@bwh.harvard.edu

SATB2 expression in uterine sarcoma: a multicenter retrospective study

Uterine sarcomas are clinically challenging because they can be difficult to diagnose and certain subtypes have a poor prognosis. The authors conducted a study to evaluate the expression of the special AT-rich sequence-binding protein 2 (SATB2) in endometrial stromal sarcoma (ESS) and other types of uterine sarcoma using IHC. They analyzed the expression of SATB2 on 71 full tissue sections of endometrial stromal nodule, low-grade ESS, uterine leiomyoma and leiomyosarcoma, undifferentiated uterine sarcoma, adenosarcoma, and carcinosarcoma samples. Nuclear SATB2 expression was then evaluated in an extended sample set, including 78 additional uterine tumor samples, using a tissue microarray. Using a cutoff of 10 percent or more of tumor cells staining as positive, the nuclear SATB2 score was negative in all (n=10) endometrial stromal nodule samples and positive in 83 percent (29 of 35) of low-grade ESS samples, 40 percent (four of 10) of undifferentiated uterine sarcoma, 13 percent (two of 16) of leiomyosarcoma, 14 percent (three of 22) of adenosarcoma, and eight percent (two of 25) of carcinosarcoma samples. Furthermore, direct comparison of nuclear SATB2 scores with clinicopathologic parameters and other reported biomarkers, such as progesterone receptor and estrogen receptor, in ESS patients showed that nuclear SATB2 was associated with progesterone receptor expression and a decreased risk of disease-specific death (odds ratio, 0.06; 95 percent confidence interval, 0.04–0.81; P=0.04). The authors' findings suggest that SATB2 could be relatively sensitive (83 percent) in distinguishing between endometrial stromal nodules and ESS and has potential prognostic value.

Le Page C, Almadani N, Turashvili G, et al. SATB2 expression in uterine sarcoma: a multicenter retrospective study. *Int J Gynecol Pathol*. 2021;40(5):487–494.

Correspondence: Dr. Kurosh Rahimi at kurosh.rahimi.chum@ssss.gouv.qc.ca

Utility of rescreening high-risk HPV-positive Pap tests initially interpreted as negative

Many laboratories rescreen Papanicolaou test slides initially interpreted as negative but positive for human papillomavirus high-risk types as a quality control measure. The authors evaluated the utility of this practice in the era of human papillomavirus (HPV) genotyping as a laboratory-improvement project. Between August 2016 and October 2019, they identified 3,618 rescreened Pap tests with follow-up biopsies. The biopsy results were grouped as negative; LSIL—HPV changes or low-grade squamous intraepithelial lesion; and HSIL—high-grade squamous intraepithelial lesion or carcinoma. HPV molecular testing results with subtyping for types 16 and 18 were available for 3,117 of these cases. A total of 530 of 2,812 (18.8 percent) Pap tests with positive HPV results were reinterpreted as cytologically abnormal after rescreening; 75 (14.2 percent) of them had a biopsy result of HSIL. The subset that was positive for HPV types 16 and 18 had 38 of 133 cytology-positive cases diagnosed as HSIL on biopsy versus 107 of 935 cytology-negative cases diagnosed as HSIL on biopsy (28.6 percent versus 11.4 percent, $P<0.0001$). The subset that was positive for other high-risk HPV types had 37 of 397 cytology-positive follow-up HSIL diagnoses versus 84 of 1,288 cytology-negative follow-up HSIL diagnoses (9.3 versus 6.5 percent, $P=0.075$). The authors concluded that rescreening has the highest yield in specimens positive for types 16 and 18. However, colposcopy is recommended for this group regardless of cytology findings, reducing the patient benefit of rescreening. Routine rescreening of cytology-negative/HPV-positive Pap tests has reduced utility when HPV subtyping is performed and should be reconsidered.

Narkcham S, Mody DR, Jones A, et al. Rescreening of high-risk HPV positive Papanicolaou tests initially screened as negative is a low yield procedure in the era of HPV genotyping. *J Am Soc Cytopathol*. 2021;10(6):558–564.

Correspondence: Dr. Michael J. Thrall at mjthrall@houstonmethodist.org

Distinguishing sarcomatoid malignant mesothelioma from benign spindle cell mesothelial proliferation

Sarcomatoid mesothelioma is an aggressive malignancy that can be difficult to distinguish from benign spindle cell mesothelial proliferations based on biopsy. This is of particular concern since the distinction is crucial to patient treatment and prognosis. A novel deep-learning–based classifier may be able to aid pathologists in making this critical distinction. The neural network-labeled SpindleMesoNet was trained on cases of malignant sarcomatoid mesothelioma and benign spindle cell mesothelial proliferations. Performance was assessed through cross-validation on the training set as well as on an independent set of challenging cases referred for expert opinion (referral test set) and an externally stained set from outside institutions (externally stained test set). SpindleMesoNet predicted the benign or malignant status of cases with an area under the receiver operating characteristic curve of 0.932, 0.925, and 0.989 on the cross-validation, referral, and external test sets, respectively. The accuracy of SpindleMesoNet on the referral set cases (92.5 percent) was comparable to the average accuracy of three experienced pathologists on the same slide set (91.7 percent). The authors concluded that SpindleMesoNet can distinguish sarcomatoid mesothelioma from benign spindle cell mesothelial proliferations. A deep-learning system of this type holds potential for future use as an ancillary test in diagnostic pathology.

Naso JR, Levine AB, Farahani H, et al. Deep-learning based classification distinguishes sarcomatoid malignant mesotheliomas from benign spindle cell mesothelial proliferation. *Mod Pathol*. 2021;34:2028–2035.

Correspondence: Dr. Andrew Churg at achurg@mail.ubc.ca